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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,473	11/08/2001	Michael Hagen	33,482-00	3152

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EXAMINER	
LE, EMILY M	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
06/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,473	HAGEN, MICHAEL	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-90,98,105,109,116-119,160,163,164 and 167* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 88-90, 98-119, 127-130, 138-141, 149-152, 160, 162-164, 166-168, 170-171, 173-174, 176-177, 179-180, 182-183 and 185-199.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 99-104, 106-108, 110-115, 127-130, 138-141, 149-152, 162, 166, 168, 170-171, 173-174, 176-177, 179-180, 182-183 and 185-199.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, the adjuvant combination of 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A and granulocyte macrophage colony stimulating factor (GM-CSF), in the reply filed on 7/31/2006 is acknowledged.

Status of claims

2. Claims 1-87, 91-97, 120-126, 131-137, 142-148, 153-159, 161, 165, 169, 172, 175, 178, 181 and 184 are cancelled. Claims 186-199 are added. Claims 88-90, 98-119, 127-130, 138-141, 149-152, 160, 162-164, 166-168, 170-171, 173-174, 176-177, 179-180, 182-183 and 185-199 are pending. Claims 99-104, 106-108, 110-115, 127-130, 138-141, 149-152, 162, 166, 168, 170-171, 173-174, 176-177, 179-180, 182-183 and 185 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/21/2004 and 01/28/05. Additionally, claims 186-199 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on 07/31/2006. Claims 88-90, 98, 105, 109, 116-119, 160, 163-164 and 167 are under examination.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 88-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulrich et al. [1] and Disis et al.[2]

In response to the rejection, Applicant submits that the Office has failed to establish a prima case of obviousness because the Office's reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the cited references teach or suggest the combination claimed at the present invention.

Applicant's submission has been considered, however, it is not found persuasive. As indicated in the previous office action, the Office cited In re Kerkhoven and MPEP § 2144.06, which provides:

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from

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[1] Ulrich et al. Monophosphoryl lipid A as an adjuvant. Past experiences and new directions. In M.F. Powell and M.J. Newman (ed.), Vaccine Design. Plenum Press, New York, NY, p. 495-523.
[2] Disis et al. Granulocyte-macrophage colony-stimulating factor: an effective adjuvant for protein and peptide based vaccines. Blood, 1996; Vol. 88, no. 1: 202-210.

their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)"

In the instant case, Ulrich et al. teaches that the immunostimulant MPL delivered in aqueous admixtures, in oil-in-water emulsions, or in liposomal vehicles has adjuvant activity. Similar to Ulrich et al., Disis et al. teaches that GM-CSF is an excellent adjuvant. Both Ulrich et al. and Disis et al. teaches two compositions, each of which is useful for the same purpose, as adjuvants. Hence, in accordance with In re Kerkhoven and MPEP § 2144.06, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose.

Applicant also noted that the adjuvant effect of MPL is formulation dependent. To support this assertion, Applicant cited Boon et al., who teaches that GM-CSF was unable to enhance the effect of the MPL adjuvant formulation containing QS21.

Applicant's submission has been considered, however, it is not found persuasive. As Applicant has indicated, GM-CSF was unable to enhance the effect of the MPL adjuvant formulation, however, the teaching of Boon et al. is limited to formulations that are similar to those constructed by Boon et al., adjuvant formulations comprising GM-CSF, MPL, **QS-21 and IL-12**. In the instant case, the adjuvant formulation of Boon et al. comprises more ingredients than those being claimed and rendered obvious by the cited art. Furthermore, as in accordance with In re Kerkhoven and MPEP § 2144.06, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. Furthermore, it is noted that the claimed composition, while limited to the presence of MPL and GM-CSF, is not limited to a

specific formulation since any diluent and/or carrier can be used. Hence, while Applicant's submission has been noted, however, it is not sufficient to overcome this rejection.

As previously presented, the claims are directed to a composition consisting of an antigen and an adjuvant, wherein the adjuvant consists of 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A, and granulocyte-macrophage colony stimulating factor (GM-CSF), together with a diluent or carrier. Claim 89, which depends on claim 88, requires the antigen to be a peptide or protein. Claim 90, which depends on claim 88, requires 3-O-deacylated monophosphoryl lipid A be used in the form of a stable oil-in-water emulsion.

Ulrich et al. teaches the use of monophosphoryl lipid A as an adjuvant to bacterial and viral protein and peptide based vaccines to enhance antibody response to said bacterial and viral protein or peptide. [Pages 509-513, in particular.] Ulrich et al. also teaches the inclusion of the adjuvant with a carrier. [Section 3.2.1, page 503, in particular.] Specifically, Ulrich et al. teaches the presentation of monophosphoryl lipid A in a stable oil-in-water emulsion. In summary, Ulrich et al. teaches that MPL alone or in combination of other vehicles or immunomodulator provides the appropriate adjuvant activities for a variety of vaccine antigens, including protein and peptide antigens.

However, Ulrich et al. does not teach the inclusion of granulocyte-macrophage colony stimulating factor (GM-CSF).

Disis et al. teaches the use of granulocyte-macrophage colony stimulating factor (GM-CSF) as a potent adjuvant for the generation of immune responses, both humoral

and cell-mediated, to foreign proteins as well as peptide-based vaccines. [Abstract, in particular.]

In the instant, both monophosphoryl lipid A and granulocyte-macrophage colony stimulating factor (GM-CSF) are art recognized adjuvants. Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine two art-recognized adjuvants into one composition. [See *In re* Kerkhoven and MPEP § 2144.06 [R-3].] One of ordinary skill in the art at the time the invention was made would have been motivated to do so to enhance the immune response against an antigen of interest. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the adjuvant activity of both monophosphoryl lipid A and GM-CSF is well recognized in the art at the time the invention was made. Therefore, the claimed invention is obvious over the teachings both Ulrich et al. and Disis et al.

6. Claims 88, 98 and 116-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulrich et al. and Disis et al., as applied to claim 88, in view of Bartlett et al.[3]

In response to the rejection, Applicant submits that the Office has failed to establish a prima case of obviousness because the Office's reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the cited references teach or suggest the combination claimed at the present invention.

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[3] Bartlett et al. Safety and immunogenicity of an HLA-based HIV envelope polyvalent synthetic peptide immunogen. AIDS, 1998, Vol. 12, No. 11, 1291-1300.

Applicant's submission has been considered, however, it is not found persuasive. As indicated in the previous office action, the Office cited In re Kerkhoven and MPEP § 2144.06, which provides:

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)"

In the instant case, Ulrich et al. teaches that the immunostimulant MPL delivered in aqueous admixtures, in oil-in-water emulsions, or in liposomal vehicles has adjuvant activity. Similar to Ulrich et al., Disis et al. teaches that GM-CSF is an excellent adjuvant. Both Ulrich et al. and Disis et al. teaches two compositions, each of which is useful for the same purpose, as adjuvants. Hence, in accordance with In re Kerkhoven and MPEP § 2144.06, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose.

Applicant also submits that Applicant's adjuvant combination elicits high titers and CTL responses.

Applicant's submission has been considered, however, it is not found persuasive. In the absence of unexpected results, it is expected that the immune response induced by both MPL and GM-CSF to be either the same or additive of one another. Furthermore, it should be noted that greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can

either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991). [MPEP 716.02(a)]

As previously presented, claim 98, which depends on claim 88, requires the antigen to be derived from a pathogenic virus. Claim 116, which depends on claim 98, requires the pathogenic virus is human immunodeficiency virus, HIV. Claim 117, which depends on claim 116, requires the HIV antigen be a protein, polypeptide or peptide. Claim 118, which depends on claim 117, further limits the HIV antigen to those having the amino acid sequence set forth in SEQ ID NO: 2. Additionally, claim 119, which depends on claim 116, requires 3-O-deacylated monophosphoryl lipid A to be in the form of a stable oil-in-water emulsion.

The significance of Ulrich et al. and Disis et al., as applied to claim 88, is discussed above. In the instant, neither Ulrich et al. nor Disis et al. teaches an HIV antigen having the amino acid sequence set forth in SEQ ID NO: 2. However, the deficiency noted in Ulrich et al. and Disis et al. is fully compensated by the teachings of Bartlett et al. Bartlett et al. teaches C4-$V3_{MN}$, which has the following sequence: KQIINMWQEVGKAMYATRPNYNKRKRIHIGPGRAFYTTK. [Immunogen design, peptide synthesis and purification section, page 1292, in particular.] In the instant, the C4-$V3_{MN}$ peptide that Bartlett et al. teaches has the same amino acid sequence as SEQ ID NO: 2, which has the following amino acid sequence: KQIINMWQEVGKAMYATRPNYNKRKRIHIGPGRAFYTTK. Bartlett et al. teaches the

use of C4-$V3_{MN}$ to elicit an HIV-antigen specific immune response. Hence, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine the adjuvant composition of Ulrich et al. and Disis et al. with the HIV antigen of Bartlett et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to enhance the immunogenicity of the HIV antigen that Bartlett et al. teaches. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the use of adjuvant to enhance the immunogenicity of antigens is routinely practiced in the art. Furthermore, the adjuvanting effects of 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A and GM-CSF, together with a carrier or a diluent has been recognized in the art at the time the invention was made. Therefore, the claimed invention is obvious over the teachings of Ulrich et al., Disis et al. and Bartlett et al.

7. Claims 88, 98, 105, 109, 116, 160, 163-164 and 167 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulrich et al. and Disis et al., in view of Bartlett et al., as applied to claims 88, 98 and 116.

In response to the rejection, Applicant submitted arguments presented in paragraphs 6-7 of this office action. A response to the arguments presented is also provided in paragraphs 6-7 of this office action.

Claims 105, 109, 160, 163-164 and 167 are directed to the administration of the composition of claims 98 (as it pertains to claims 105 and 109) and 116 (as it pertains to claims 160, 163-164 and 167) to elicit an immune response in a subject. In the instant,

claim 105 and 109 recite a direct dependency to claim 98, which depends on claim 88; and claims 160 and 164 recite a direct dependency to claim 116, which depends on claim 98. Additionally, claim 163 recites a dependency to claim 160; and claim 167 recites a dependency to claim 164. In addition to eliciting an immune response in the subject, claims 109 and 164 requires that the immune response be a CTL response. Lastly, claims 163 and 167 require the antigen administered to have the amino acid sequence set forth in SEQ ID NO: 2.

The significance of Ulrich et al., Disis et al. and Bartlett et al., as applied to claims 88, 98 and 116, is discussed above. In the instant, Ulrich et al., Disis et al. and Bartlett et al. do not teach the administration of the composition of claims 98 and 116; however, as discussed above, the antigen of Bartlett et al. is a multideterminant peptide comprising T-helper epitopes from the fourth constant region (C4) of gp120 of HIV-1_{MN}, and T-helper, and cytotoxic T-lymphocyte HLA-B7-restricted; and B-cell neutralizing epitopes from the gp120 third variable region. Bartlett et al. teaches the administration of the multideterminant peptide to induce an HIV specific immune response. Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to administer the HIV antigen of Bartlett et al. with the adjuvant composition that Ulrich et al. and Disis et al. teaches. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to enhance the immunogenicity of the HIV antigen that Bartlett et al. teaches. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the use of adjuvant to enhance the immunogenicity of

antigens is routinely practiced in the art. Furthermore, the adjuvanting effects of 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A and GM-CSF, together with a carrier or a diluent has been recognized in the art at the time the invention was made. Therefore, the claimed invention is obvious over the teachings of Ulrich et al., Disis et al. and Bartlett et al.

Additionally, the administration of the antigen of Bartlett et al. would necessarily induce a CTL response in the subject. As noted above, the antigen of Bartlett et al. contains CTL specific epitopes. Thus, the administration of said antigen would necessarily induce a CTL response in the subject.

Conclusion

8. No claims are allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bruce R. Campell/
Bruce R. Campell
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/E.Le/